Palm dermatoglyphs and interleukin-4 receptor polymorphisms in asthma

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Abstract. Single nucleotide polymorphisms (SNPs) in the interleukin-4 receptor (IL-4R) gene have been identified as having a close association with asthma severity in different populations. In our previous studies, a close association between asthma and a distinctive palm dermatoglyphic pattern was observed; however, the clinical implication and underlying genetic mechanisms of this particular palm pattern have not been clarified. Whether this particular palm pattern is associated with asthma severity and IL-4R SNPs was assessed in the present study. A case cohort study was conducted in 400 patients with allergic asthma and in 200 healthy controls. DNA was extracted from peripheral blood leukocytes for analysis of 11 IL-4R SNPs associated with asthma via polymerase chain reaction. There are two SNPs, rs1805012 and rs3024608, which are associated with asthma (rs1805012, dominant model; P=0.03 and rs3024608, codominant model; P=0.029), and two SNPs, rs1805010 and rs3024608, which are associated with the positive palm pattern (rs1805010, log-additive model; P=0.031 and rs3024608, codominant model; P=0.016). The SNP of rs3024608 is associated with asthma and the positive palm pattern. Thus, genetic variation in IL-4R may be associated with the development of asthma and the distinctive palm pattern; however, further investigations are required to identify the connection between asthma and palm dermatoglyphic patterns.

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Abbreviations: SNP, single nucleotide polymorphisms; IL-4, interleukin-4; IL-13, interleukin-13; IL-4R, interleukin-4 receptor; GINA, Global Initiative for Asthma; ADAM33, a disintegrin and metalloprotein-33; PCR, polymerase chain reaction

Key words: asthma, interleukin, polymorphisms, palm, dermatoglyphics

Introduction

Since last century, the prevalence of asthma has increased worldwide, which has resulted in substantial morbidity and healthcare costs (1). Patients with different phenotypes have different outcomes and prognoses. The most effective treatment strategy to effectively control asthma, as suggested by the Global Initiative for Asthma (GINA), is to implement personalized treatment according to the different phenotypes of asthma. However, it is difficult to correctly and rapidly identify the phenotype using simple clinical features, without complicated or invasive examinations.

Genetic susceptibility is critical in the development of asthma; therefore, it is often used to identify the phenotypes of asthma. Interleukin-4 receptor (IL-4R) is important in regulating T helper (Th)2 cell development and immunoglobulin E (IgE) production via its response to IL-4 or IL-13 (2). The loci of IL-4R, located on genomic region 16p12, are linked to asthma phenotypes with increased airway mast cells and IgE (+) cells. Numerous single nucleotide polymorphisms (SNPs) in IL-4R gene have been associated with a phenotype of severe asthma (3,4). However, sequencing the IL-4R gene for every patient is not considered a feasible method of differentiating the phenotypes of asthma.

In the past two decades, the value of palm dermatoglyphic or fingerprint patterns has been described in the detection of bronchial asthma by different studies; however, the underlying mechanisms have not been clarified (5-8). In our previous study, a distinctive palm pattern was identified, which was characterized by deep grids in the thenar area that facilitated the diagnosis of asthma, with a close association to two a disintegrin and metalloprotein-33 (ADAM33) gene polymorphisms (9). The palm pattern appears to be a potential biomarker for endotypes of asthma, although the association between distinctive palm patterns and other SNPs associated with asthma have yet to be investigated.

Thus, in the present study, 11 SNPs of the IL-4R gene were analyzed in a population of East Chinese Han adults to clarify the link between a particular palm pattern and IL-4R gene polymorphisms.

Materials and methods

Subjects. A total of 400 asthma patients were recruited from the pulmonary clinics of two teaching hospitals, Qingdao Municipal Hospital (Qingdao, China) and Qingdao Haici Hospital (Qingdao, China) from January 2011 to January 2012 successively. Asthma was diagnosed and evaluated based on symptoms and on spirometry assessments by the criteria of the Global Initiative for Asthma (version: 2010 update) (10). Two-hundred healthy adults were recruited successively from the Health check-up centers of Qingdao Municipal Hospital and Qingdao Haici Hospital to serve as healthy controls. All control subjects were asymptomatic for asthma and devoid of any atopic or pulmonary diseases. Pregnant or lactating female subjects were excluded. The age range for all of the study subjects was 18-70 years old. Smoking status and education history data were collected for all subjects. The study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of Qingdao Municipal Hospital and Qingdao Haici Hospital. In addition, all subjects provided written informed consent prior to the study.

Dermatoglyphic palm patterns. The palms of each subject were observed, after washing clean with soap and water, by two researchers under natural light. The palm patterns were determined by the dermatoglyphic variables in the thenar area, including number and shape of the ridges, as described in our previous study (9). A positive palm pattern typically exhibited an increased ridge count (≥10) and deep grid patterns in the thenar area, while a negative palm pattern demonstrated normal ridge count (<10) and light grid patterns in the thenar area. All subjects were sub-categorized into two groups; a positive palm pattern group and a negative palm pattern group according to the above standard.

Polymorphism genotyping. Whole blood (10 ml) was taken in lithium heparin-coated test tubes from each subject and immediately centrifuged at 1,600 x g. Buffy coat (peripheral white cells) was separated and stored at -70˚C on the day of enrollment by a nurse. Genomic DNA was isolated from the peripheral blood leukocytes using a DNA extraction kit (Tiangen Biotech Co., Ltd., Beijing, China). The DNA was genotyped for the SNPs of the IL-4R gene at the Center for Human Genetics Research, Shanghai Genesky Bio-Tech Co., Ltd. (Shangai, China). Three SNPs of the IL-4R gene, rs1805010, rs1805012 and rs1801275, were selected according to the published literatures regarding SNP associations with asthma (11,12). Eight tag SNPs, rs3024608, rs1110470, rs3024685, rs3024619, rs2057768, rs3024585, rs12925861, and rs3024613, were then selected according to the frequency information for Chinese populations from two public databases the International HapMap Project (http://www.hapmap.org/) and the NCBI database (http://www.ncbi.nlm.nih.gov/). The PCR primers were designed by the authors and are presented in Table I.

Polymerase chain reaction (PCR) amplification of the corresponding genomic region surrounding each SNP locus was performed in a Takara PCR thermal cycler (Takara TP600; Takara Biotechnology Co., Ltd., Dalian, China). The reaction was performed in a final volume of 10 μl, including 3.0 mM Mg^{2+}, 0.3 mM dNTP, 1 unit HotStarTaq polymerase (Qiagen Inc., Valencia, CA, USA), 1 μl of each primer, and 1 μl (10 ng) of genomic DNA. The cycling conditions were as follows: 1 Cycle at 95˚C for 2 min, 11 cycles at 94˚C for 20 sec, 65-0.5˚C for 40 sec and 72˚C for 1.5 min, and 24 cycles at 94˚C for 20 sec, 59˚C for 30 sec and 72˚C for 1.5 min, and a final extension at 72˚C for 2 min. The PCR products were purified using a PCR purification kit containing 1unit Shrimp Alkaline Phosphatase (SAP) and 1 unit Exonuclease I (Qiagen GmbH, Hilden, Germany) and were used as DNA templates for the cycle sequencing. Direct DNA sequencing was performed using 5 μl SNaPshot Multiplex kit (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA) in 10-μl volumes containing 2 μl primer and 2 μl DNA template, and were subjected to 1 cycle at 96˚C for 1 min, 28 cycles of denaturation at 96˚C for 10 sec, annealing at 52˚C for 5 sec, and extension at 60˚C for 30 sec. Sequencing products were purified using 1 unit SAP at 37˚C for 1 h and annealing at 75˚C for 15 min. All SNPs were detected with an ABI 3130xl, and the data were analyzed with GeneMapper 4.0 (Applied Biosystems; Thermo Fisher Scientific, Inc.). The association analysis between a single SNP and phenotype were conducted under five different genetic models (inheritance patterns) as follows: Codominant, dominant, recessive, overdominant and log-additive.

Statistical analysis. The differences in age, gender, body mass index (BMI), smoking status and education history between patients and control subjects were compared using the χ^2 test or a t-test accordingly. The correlation between palm patterns and asthma severity was evaluated by Spearman analysis. The odds ratios (ORs) and 95% confidence interval (CI) of asthma risk of individuals with various genetic polymorphisms were calculated using logistic regression analysis adjusting for differences in gender. Hardy-Weinberg equilibrium and linkage disequilibrium was estimated using SNPAnalyzer version 2.0 (Istech Corp., Korea; http://istech21.com/). Statistical analyses were conducted using the SPSS for Windows version 17.5, statistical package (SPSS, Inc, Chicago, IL, USA) and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographics. The demographics of the asthma group and the control group are presented in Table II. No significant differences were identified between the age, gender, BMI, smoking status, and education history of the asthma and control groups (all $P>0.05$).

Polymorphisms with asthma. All genotype frequencies were consistent with Hardy-Weinberg equilibrium ($P>0.05$). The genotype distributions of all 11 IL-4R SNPs in the asthma and control groups are listed in Table III. There are two SNPs, rs1805012 and rs3024608, which are associated with asthma in different models as follows: rs1805012, dominant model ($P=0.03$) and rs3024608, codominant model ($P=0.029$).

Table I. Oligonucleotide primers used for resequencing interleukin-4 receptor.

	Oligonucleotide primers	
SNP	Forward	Reverse
rs1805010	CAGCCAGCCTACAGGTGACCA	CTGACCACGTCATCCATGAGCA
rs1805012	GGAGAGGAGAATGGGGGCTTTT	ACTTGGCTCCAGGTGGAGAG
rs1801275	AGATCCTCCGCCGAAATGTCCT	ACCCTGCTCCACCGCATGTA
rs3024608	CAGCCAGGAAGTGGTAGTAGGGACT	TCGTTAGCTGACCCCACCATGT
rs1110470	AGCCTTCACTGGCTCCCCACT	GGAGAAGGACTGGCTGGGATG
rs3024685	ATGCCCTAACCTCCCAGGAATG	TACCCCAGCTCCCTCTCCTTTG
rs3024619	AGAACTACAGAGGAAACTAATTGTATTGAAATG	TCCTGTCCCCAGCAAAACAAAA
rs2057768	CCCTAGATGGGGGAACAGAGGTT	GCATTGTTCTCGGGTGCAAGAG
rs3024585	CCACCTTCAGAGTCCAAAGATATGTTATTT	CATGAGGGAAGAGCCTGCCTAAA
rs12925861	AAGCTGCCCACTGCTTAGAGGA	TCATGGGTCTTAAATCCAGCACTCA
rs3024613	CAGACACTTCCCCTGGCTGAGT	CAGGGAGGGAAACCACCTACAA

SNP, single nucleotide polymorphism.

Table II. Demographics of asthma patients and healthy control subjects (presented as means ± standard deviation).

Variable	Asthma (n=400)	Control (n=200)	t	χ^2	P-value
Age, years	40.11±14.54	45.42±16.28	0.35	-	>0.05
Body mass index, kg/m^2	24.78±3.22	24.51±3.40	0.09	-	>0.05
Gender			-	1.98	>0.05
Male	172	74			
Female	228	126			
Smoking			-	0.50	>0.05
Smoker[a]	115	52			
Non-smoker	285	148			
Education, years	15.24±8.13	15.89±8.81	0.08	-	>0.05

[a]Current and previous smokers.

Table III. Genotype of interleukin-4 receptor SNPs in the asthma and control groups (adjusted for gender and age).

SNP	Genotype	Control, n (%)	Asthma, n (%)	Odds ratio (95% CI)	P-value
rs2057768	T/T	63 (31.50	115 (28.97)	1	0.96
	C/T	93 (46.50)	195 (49.11)	1.06 (0.68-1.65)	
	C/C	44 (22.00)	87 (21.91)	1.07 (0.62-1.84)	
rs1110470	G/G	85 (42.50)	161 (40.25)	1	0.59
	G/A	93 (46.50)	183 (45.75)	0.97 (0.65-1.47)	
	A/A	22 (11.00)	56 (14.00)	1.34 (0.71-2.50)	
rs12925861	A/A	58 (29.00)	111 (27.80)	1	0.94
	A/T	95 (47.50)	201 (50.20)	1.03 (0.66-1.62)	
	T/T	47 (23.50)	88 (22,00)	0.95 (0.55-1.62)	
rs1805010	G/G	54 (27.14)	112 (28.14)	1	0.75
	G/A	99 (49.75)	201 (50.50)	0.88 (0.56-1.38)	
	A/A	46 (23.12)	85 (21.36)	0.82 (0.48-1.41)	
rs3024585	A/A	88 (44.22)	173 (43.57)	1	0.78
	G/A	89 (44.72)	182 (45.84)	0.91 (0.60-1.36)	
	G/G	23 (11.56)	42 (10.57)	0.81 (0.43-1.53)	

Table III. Continued.

SNP	Genotype	Control, n (%)+	Asthma, n (%)	Odds ratio (95% CI)	P-value
rs3024608	C/C	161 (80.50)	340 (85.56)	1	0.03
	C/G	39 (19.50)	53 (13.35)	0.56 (0.33-0.94)	
	G/G	0 (0)	4 (1.01)	NA (0.00-NA)	
rs3024613	C/C	56 (28.28)	99 (25.00)	1	0.39
	C/T	95 (47.98)	208 (52.53)	1.37 (0.86-2.18)	
	T/T	47 (23.73)	89 (22.47)	1.15 (0.67-1.99)	
rs3024619	G/G	68 (34.00)	122 (30.73)	1	0.51
	G/A	95 (47.50)	205 (51.64)	1.26 (0.82-1.95)	
	A/A	37 (18.50)	70 (17.63)	1.02 (0.58-1.79)	
rs1805012	T/T	169 (84.50)	361 (90.93)	1	0.03
	C/T	31 (15.50)	35 (8.82)	0.50 (0.27-0.90)	
	C/C	0 (0)	1 (0.25)	NA (0.00-NA)	
rs1801275	A/A	141 (70.50)	281 (70.78)	1	0.47
	G/A	51 (25.50)	108 (27.20)	0.97 (0.62-1.51)	
	G/G	8 (4.00)	8 (2.05)	0.48 (0.15-1.53)	
rs3024685	C/C	67 (33.50)	133 (33.25)	1	0.87
	C/T	97 (48.50)	194 (48.50)	0.90 (0.59-1.38)	
	T/T	36 (18.00)	73 (18.25)	0.90 (0.51-1.58)	

SNP, single nucleotide polymorphism; CI, confidence interval.

Table IV. Genotype of interleukin-4 receptor SNPs in the negative and positive palm pattern groups (adjusted for gender and age).

SNP	Genotype	Negative palm, n (%)	Positive palm, n (%)	Odds ratio (95% CI)	P-value
rs1805010	G/G	81 (25.55)	85 (30.4)	1	0.031
	G/A	157 (49.53)	143 (51.1)	0.79 (0.52-1.19)	
	A/A	79 (24.92)	52 (18.6)	0.58 (0.35-0.95)	
rs1805012	T/T	282 (88.68)	248 (88.9)	1	0.47
	C/T	36 (11.32)	30 (10.8)	1.10 (0.62-1.94)	
	C/C	0 (0)	1 (0.4)	NA (0.00-NA)	
rs1801275	A/A	228 (71.69)	194 (69.53)	1	0.42
	G/A	83 (26.10)	76 (27.24)	1.04 (0.70-1.55)	
	G/G	7 (2.21)	9 (3.23)	2.15 (0.67-6.84)	
rs3024608	C/C	264 (83.02)	237 (84.95)	1	0.02
	C/G	54 (16.93)	38 (13.62)	0.73 (0.44-1.19)	
	G/G	0 (0)	4 (1.43)	NA (0.00-NA)	
rs1110470	G/G	121 (37.93)	125 (44.48)	1	0.2
	G/A	155 (48.58)	121 (43.06)	0.71 (0.49-1.04)	
	A/A	43 (13.48)	35 (12.45)	0.79 (0.46-1.38)	
rs3024685	C/C	106 (33.22)	94 (33.45)	1	0.96
	C/T	154 (48.27)	137 (48.75)	0.97 (0.66-1.44)	
	T/T	59 (18.50)	50 (17.79)	0.93 (0.56-1.54)	
rs3024619	G/G	105 (33.02)	85 (30.46)	1	0.49
	G/A	161 (50.63)	139 (49.82)	1.10 (0.74-1.64)	
	A/A	52 (16.45)	55 (19.71)	1.36 (0.82-2.28)	
rs2057768	T/T	89 (27.99)	89 (31.90)	1	0.44
	C/T	153 (48.11)	135 (48.38)	0.85 (0.57-1.28)	
	C/C	76 (23.90)	55 (19.71)	0.73 (0.44-1.19)	

Table IV. Continued.

SNP	Genotype	Negative palm, n (%)	Positive palm, n (%)	Odds ratio (95% CI)	P-value
rs3024585	A/A	131 (41.19)	130 (46.59)	1	0.19
	G/A	150 (47.17)	121 (43.37)	0.74 (0.51-1.08)	
	G/G	37 (11.64)	28 (10.04)	0.66 (0.37-1.19)	
rs12925861	A/A	84 (26.33)	85 (30.25)	1	0.14
	A/T	153 (47.96)	143 (50.89)	0.88 (0.58-1.33)	
	T/T	82 (25.71)	53 (18.86)	0.62 (0.37-1.01)	
rs3024613	C/C	78 (24.68)	77 (27.70)	1	0.65
	C/T	163 (51.58)	140 (50.36)	0.86 (0.56-1.31)	
	T/T	75 (23.73)	61 (21.44)	0.80 (0.48-1.32)	

SNP, single nucleotide polymorphism; CI, confidence interval.

Polymorphisms with palm patterns. The genotype distribution of all 11 IL-4R SNPs in the negative and positive palm groups are presented in Table IV. Two SNPs, rs1805010 and rs3024608, were associated with the positive palm pattern in different models as follows: rs1805010, log-additive model (P=0.031) and rs3024608, codominant model (P=0.016). Notably, rs3024608 is associated with asthma and the positive palm pattern. The rs1805010, rs1805012 and rs3024608 with different genotypes are presented in Fig. 1.

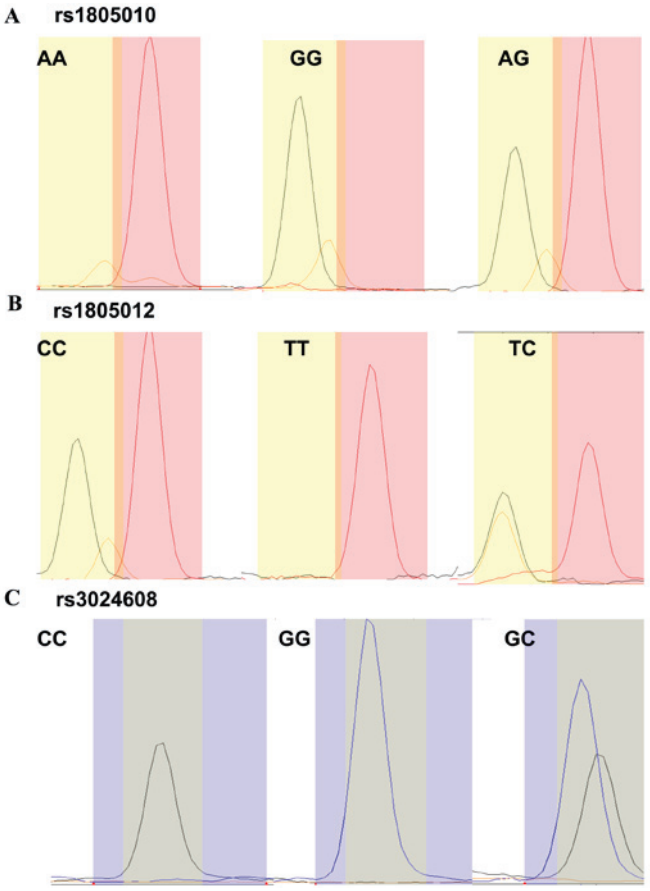

Figure 1. Different genotypes of rs1805010, rs1805012 and rs3024608. (A) AA, GG and AG genotypes of rs1805010; (B) CC, TT and TC genotypes of rs1805012; (C) CC, GG and GC genotypes of rs3024608.

Discussion

In the present study, gene segments of 11 SNPs of the IL-4R gene were amplified to identify the genetic basis of the association between a distinctive palm dermatoglyphic pattern and asthma in a Chinese population.

As the results of SNP studies are not always consistent in different populations, the present study evaluated the role of SNPs of IL-4R in asthma development in the Chinese population. Although three SNPs, rs1801275 (-1902G/A), rs1805012 (1291T/C) and rs1805010 (-223G/A) demonstrated associations with asthma in previous studies (11-13), only rs1805012 exhibited an association with asthma (dominant model; P=0.03) in the current study. To further investigate the effect of IL-4R SNPs in asthma, eight tag SNPs of the IL-4R region were investigated for an association with asthma, to the best of our knowledge, for the first time. Of these SNPs, two were associated with asthma in a different model: rs1805010, log-additive model (P=0.031) and rs3024608, codominant model (P=0.016). Thus, polymorphisms of the IL-4R gene may be the genetic basis of asthma in this particular population.

Dermatoglyphs are formed in the 10th to 17th weeks of the embryological phase, when the neurologic and immunity systems are developing. Generally dermatoglyphs remain unchanged throughout an individual's life, except in cases of serious injuries that scar the dermis. Thus, a series of studies have identified the association of dermatoglyphic patterns with certain congenital defects or gene-associated diseases, such as Down's syndrome (14-17). However, few practical associations have been recognized in humans. Palm patterns are affected by many complex factors, for example age-associated changes, gender and ethnic differences. A distinctive palm pattern was identified in asthma patients using theories of Chinese Traditional Medicine (5). However, it is difficult to confirm the clinical significance of these dermatoglyph changes in clinical practice.

As asthma is a disorder associated with multiple genetic factors, establishing the gene polymorphisms associated with asthma is considered to be a convictive method to elucidate

the implications of the association between a distinctive palm pattern and asthma. In our previous study, two SNPs of ADAM33, rs44707 and rs2787094, were identified to be associated with a positive palm pattern (6). In the current study, of 11 analyzed SNPs of IL-4R, two SNPs were found to be associated with the distinctive palm pattern in different models (rs1805010: Log-additive model, P=0.031; rs3024608: Codominant model, P=0.016). Notably, rs3024608 was associated with the positive palm pattern and asthma in the same population; thus, IL-4R polymorphisms may be the genetic basis of the association of the distinctive palm pattern and asthma.

Recently Chavarri-Guerra and Soto-Perez-de-Celis (14) described a 65-year-old woman with stage IV breast cancer, who lost her fingerprints following chemotherapy with capecitabine and bevacizumab (18). This indicated that dermatoglyphs may change as a condition of the disease (19,20). The clinical significance of dermatoglyphs requires further clarification using well-designed studies.

In conclusion, the genetic variation in IL-4R may be the basis of the association between asthma and a distinctive palm pattern. Considering the genetic variant, further studies with a prospective design in an unselected population are required to validate the association between a distinctive palm pattern and asthma, in order that a distinctive palm pattern may be considered as a biomarker for asthma development or phenotypes (21).

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